REMARKS

Claims 37-56 and 74-78 stand rejected. In view of the following remarks, Applicants respectfully request reconsideration and allowance of claims 37-56 and 74-78.

Foreign Priority

The Examiner noted that translations of the priority documents (PCT/EP03/02084 and DE10209822.0) have not been provided to the Patent and Trademark Office. Applicants are working to obtain English translations of these documents.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 37-45, 47, 48, 50, 52, 56, and 74-78 under 35 U.S.C. § 102(b) as allegedly being anticipated by published Canadian Application No. 2233725 (the Adamson publication). The Examiner alleged that the Adamson publication discloses conjugates prepared by reacting hemoglobin with oxidized hydroxyethyl starch (HES), allowing the resulting conjugate to degrade to a lower molecular weight product, and reductively stabilizing the conjugate to form secondary amino bonds between the hemoglobin and the HES. The Examiner further alleged that the Adamson publication anticipates the presently claimed conjugates of HES with a low molecular weight substance.

Applicants respectfully disagree. The Adamson publication does not disclose all limitations recited in the present claims. The present claims recite a conjugate of hydroxyalkyl starch (HAS) and a low molecular weight substance, characterized in that the binding interaction between the HAS molecule and the low molecular weight substance is based on a covalent bonding which is the result of a coupling reaction between (i) the terminal aldehyde group, or a functional group derived from this aldehyde group by chemical reaction, of the HAS molecule and (ii) a functional group, which is able to react with this aldehyde group or functional group derived therefrom of the HAS molecule, of the low molecular weight substance. Thus, the conjugates recited in the present claims are formed via the terminal aldehyde group of HAS. In contrast, the Adamson publication discloses HAS-hemoglobin conjugates obtained by reacting aldehyde groups of an oxidized HAS with an amine function of hemoglobin, forming a Schiff

base. The conjugates of Adamson are disclosed to be formed by conjugating hemoglobin to HAS that has been unspecifically modified with aldehyde groups (i.e., modified with aldehyde groups at different positions of the HAS molecule). Such unselective modification of HAS is disclosed to be achieved by initially oxidizing various available diol groups of the polysaccharide by a ring opening reaction using periodate as an oxidizing agent, wherein the oxidation yields in a mixture of unspecifically oxidized HAS molecules. *See*, for example, page 8, lines 12-21, and page 11, lines 22-24 of the Adamson publication. At no point does the Adamson publication disclose a method in which hemoglobin is selectively coupled to the terminal aldehyde group of HAS.

Further, and contrary to the Examiner's position, the Adamson publication does not disclose conjugating a low molecular weight substance to HES. Rather, the hemoglobin that is conjugated to HES as described by Adamson has a molecular weight 64 kDa (*see*, page 1, lines 25-30). Although the initially formed conjugate is allowed to degrade, Applicants submit that it is not the protein portion of the conjugate that is degrading. Rather, some of the Schiff base interactions between the hemoglobin and the HES are allowed to hydrolyze, resulting in a final product with a molecular weight that is less than that of the initially formed conjugate.

In addition, Applicants note that the Adamson publication does not disclose all of the limitations recited in the instant dependent claims. For example, at no point does the Adamson publication disclose the use of a linker, much less a bifunctional linker as recited in present claims 38 and 39. Further, at no point does the Adamson publication disclose an amide linkage between a low molecular weight substance and HAS, as recited in present claim 41. Thus, the Adamson publication does not disclose all limitations of the instantly rejected claims.

For at least these reasons, the Adamson publication fails to anticipate the present claims. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 37-45, 47, 48, 50, 52, 56, and 74-78 under 35 U.S.C. § 102(b).

The Examiner rejected claims 37-45, 47-56, and 74-78 under 35 U.S.C. § 102(b) as allegedly being anticipated by EP Patent No. 0 331 471 (the Larsen et al. patent; referred to by the Examiner as the Harboe et al. patent). The Examiner alleged that the Larsen et al. patent discloses anti-inflammatory prodrugs of the formula PS-O-A-(CH_2)n-B-D, wherein PS-OH can

be HES, A is CO or a direct bond, N is 0 to 14, B is O, CO, NR, or a direct bond, R is H or a lower alkyl, D is R_1CO or R_2O, and R_1COOH and R_2OH are anti-inflammatory agents. The Examiner further alleged that the Larsen et al. patent discloses a list of anti-inflammatory prodrugs that can be used in the formula, and also discloses that the prodrugs can be used to treat particular clinical conditions, and thus anticipates a pharmaceutical composition as recited in claim 56, as well as some of the drugs recited in claims 49, 51, 53, and 55.

Applicants respectfully disagree. Again, the present claims recite conjugates formed via the terminal aldehyde group of HAS. The Larsen et al. patent discloses anti-inflammatory prodrugs of the formula PS-O-A-(CH_2)n-B-D, wherein PS-OH can be HAS. In these prodrugs, the HAS is disclosed to be conjugated to the anti-inflammatory drug via any free hydroxyl group present in the starch molecule. Thus, a mixture of conjugates is obtained, which are formed by statistically reacting any free hydroxyl group of the polysaccharide with a suitable functional group of the drug. The Larsen et al. patent contains no teaching whatsoever with regard to linking an aldehyde group of HAS to an active agent, much less any teaching with regard to linking the terminal aldehyde group of HAS to an active agent. Since the Larsen et al. patent fails to disclose either a conjugate in which a protein is attached to the terminal aldehyde group of HAS, or a process for making such a conjugate, this patent does not anticipate the present claims.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 37-45, 47-56, and 74-78 under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103

The Examiner rejected claims 37-45, 47, 48, 50, 52, 56, and 74-78 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Adamson publication or the Larsen et al. patent or EP Patent No. 019403 (the Berger et al. patent) in view of U.S. Patent No. 5,502,043 (the Weidler et al. patent). The Examiner referred to the Adamson publication and the Larsen et al. patent as described above. The Examiner further asserted that the Berger et al. patent discloses a HAS drug that can be linked to a biologically active compound, and "embraces the description of the bonding of the [HAS] to the low molecular weight substance of the instant claims." In addition, the Examiner alleged that although the conjugate of the present claims differs from the

conjugates of Adamson, Larsen et al., and Berger et al. by claiming that the HAS molecule has a ratio of C_2 to C_6 substitution of 8 to 12, the Weidler et al. patent discloses using HES for improvement of microcirculation and shows that the C_2/C_6 ratio of a HAS that covers the presently recited range was known in the art. Finally, the Examiner alleged that it would have been obvious to a person of ordinary skill in the art at the time the present invention was made to substitute the HAS of Adamson, Larsen et al., or Berger et al. with the HAS of Weidler et al.

Applicants respectfully disagree. None of the combinations asserted by the Examiner render the present claims obvious. First, as discussed above, the Adamson publication fails to disclose conjugates between HAS and a low molecular weight substance, much less a conjugate between HAS and a low molecular weight substance in which the two components are linked via the terminal aldehyde group of the HAS. Second, the Larsen et al. patent also fails to disclose a conjugate in which HAS is linked to another molecule via the terminal aldehyde group of HAS, as discussed above. Third, the Berger et al. patent contains no teaching with regard to functionalizing or coupling a low molecular weight substance to the terminal aldehyde group of HAS. In fact, the Berger et al. patent discloses that HAS can be coupled to another compound via any of its free hydroxyl functions, which are described as "useful sites for bonding active compounds." *See*, e.g., page 3, line 63 to page 4, line 3. In this context, the Berger et al. patent discloses various methods for activating hydroxyl groups (e.g., by unselective oxidation or by functionalization with cyanogen bromide), all of which yield a mixture of unspecifically modified HAS molecules.

The Weidler et al. patent fails to disclose any conjugate of HAS and another molecule, and thus does not remedy the deficiencies of the Adamson publication, the Larsen et al. patent, and the Berger et al. patent. For at least these reasons, a person of ordinary skill in the art at the time of Applicants' priority date, reading the Weidler et al. patent in combination with either the Adamson publication, the Larsen et al. patent, or the Berger et al. patent, would not have been motivated to make a HAS conjugate as recited in the present claims. Thus, the cited combinations of references do not render the present claims obvious.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 37-45, 47, 48, 50, 52, 56, and 74-78 under 35 U.S.C. § 103(a).

Inventorship

Applicants respectfully request correction of the inventorship for the present application. The Assignee has determined that Klaus Sommermeyer, Wolfram Eichner, Sven Frie, Katharina Lutterbeck, Cornelius Jungheinich, and Roland Scharpf should be added as inventors. Thus, the attached declaration lists the above-named individuals as inventors, in addition to Jurgen Hemberger and Michele Orlando. Also submitted herewith are an assignment from the added inventors to the real party in interest (Fresenius Kabi Deutschland GmbH), a statement from the Assignee consenting to the correction of inventorship, and a declaration by the added inventors that their omission from the previous list of inventors was without deceptive intent.

CONCLUSION

Applicants submit that claims 37-56 and 74-78 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please charge $1110 for the Petition for Extension of Time fee, and apply any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

Date:/December 15, 2008/

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